

***Remarks***

Reconsideration of this Application is respectfully requested.

A Request for Continuing Prosecution under 37 C.F.R. § 1.114 is being filed herewith, such that the finality of the Office Action will be withdrawn. Accordingly, it is not believed necessary to provide reasons why the foregoing amendment should be entered.

Upon entry of the foregoing amendment, claims 10-15, 17-21 and 34-52 are pending in the application, with claims 10 and 52 being the independent claims. Claims 10 and 52 have been amended and claims 22-33 have been canceled without prejudice or disclaimer of the subject matter therein.

Support for the amendment of claims 10 and 52 is found in the Specification at page 4, lines 20-21; page 5, lines 1-2; page 6; lines 19-20; and page 8, line 29 to page 9, line 4.

These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the following remarks, Applicant respectfully requests that the Examiner reconsider and withdraw all of outstanding objections and rejections.

***Rejection Under 35 U.S.C. § 112, First Paragraph***

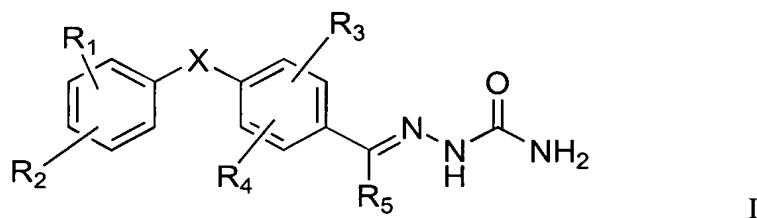
The Examiner has rejected claims 10-15, 17-21, 34-35 and 50-52 under 35 U.S.C. § 112, first paragraph, as allegedly not enabled. Applicant respectfully traverses this rejection.

The Examiner stated:

[T]he specification while being enabling for the treatment of neuropathic pain with 1.25 mg/kg of 4-(4'-fluorophenoxy)benzaldehyde semicarbazone and 25 mg/kg of gabapentin, does not reasonably provide enablement for "treating or ameliorating neuropathic pain . . . a sodium channel blocker and a second agent selected from the group consisting of gabapentin, pregabalin, salts thereof and combination thereof . . ." . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Office Action at page 3. Applicant respectfully disagrees.

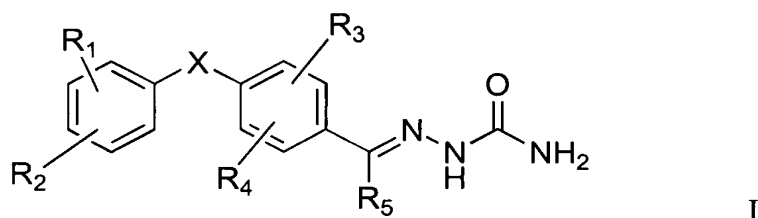
Independent claim 10 has been amended to recite: "[a] method of treating or ameliorating neuropathic pain, comprising administering to a patient in need thereof a first agent which is a semicarbazone represented by Formula I



where R<sub>1</sub>-R<sub>4</sub> are independently hydrogen, halogen, C<sub>1-9</sub> alkyl, C<sub>3-9</sub> cycloalkyl, cyano, C<sub>1-9</sub> alkoxy, or C<sub>6-10</sub> aryloxy; R<sub>5</sub> is hydrogen, C<sub>1-9</sub> alkyl, C<sub>3-9</sub> cycloalkyl, or C<sub>6-10</sub> aryl; and X is oxygen or sulfur; and a second agent selected from the group consisting of gabapentin, pregabalin, salts thereof and combinations thereof; wherein said first agent

and said second agent are present in synergistic amounts effective to treat or ameliorate neuropathic pain."

Independent claim 52 has been amended to recite: "[a] method of treating or ameliorating neuropathic pain, comprising administering substantially simultaneously to a patient in need thereof a semicarbazone represented by Formula I



where R<sub>1</sub>-R<sub>4</sub> are independently hydrogen, halogen, C<sub>1-9</sub> alkyl, C<sub>3-9</sub> cycloalkyl, cyano, C<sub>1-9</sub> alkoxy, or C<sub>6-10</sub> aryloxy; R<sub>5</sub> is hydrogen, C<sub>1-9</sub> alkyl, C<sub>3-9</sub> cycloalkyl, or C<sub>6-10</sub> aryl; and X is oxygen or sulfur; and at least one of gabapentin and pregabalin, wherein said semicarbazone and at least one of gabapentin and pregabalin are administered in synergistic amounts effective to treat or ameliorate neuropathic pain."

Formula I in claims 10 and 52 encompasses semicarbazones, one of which, 4-(4'-fluorophenoxy)benzaldehyde semicarbazone, is shown in Example 1 of the present Specification to exhibit a synergistic effect with gapapentin in treating neuropathic pain.

Given the knowledge possessed by one of ordinary skill in the art and the teachings of the present Specification, one of ordinary skill in the art could have determined synergistic amounts of the first and second agent to be administered to treat or ameliorate neuropathic pain.

Referring to WO 03/020273, the Examiner stated at page 4 of the office action that "not all of dosage range [sic] of combination of 4-(4'-fluorophenoxy)benzaldehyde

semicarbazone and gabapentin provide the synergistic effects." This disclosure in WO 03/020273 is believed to be irrelevant to the claimed methods. WO 03/020273 tested 4-(4'-fluorophenoxy)benzaldehyde semicarbazone and gabapentin in a model of inflammatory pain. In contrast to WO 03/020273, the claimed methods relate to treatment and amelioration of neuropathic pain. The results obtained in WO 03/020273 with a combination of 4-(4'-fluorophenoxy)benzaldehyde semicarbazone and gabapentin in an inflammatory pain model, while useful for determining anti-nociceptive activity, are not predictive of what will happen in a subject with neuropathic pain. The Chung model, see Example 1 of the present specification, is an accepted model of neuropathic pain.

One of ordinary skill in the art could have practiced the claimed methods without undue experimentation. Therefore, the claimed methods are enabled. Applicant respectfully requests that this rejection be reconsidered and withdrawn.

***Rejection Under 35 U.S.C. § 112, Second Paragraph***

The Examiner has rejected claim 17 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Applicant respectfully traverses this rejection.

Claim 17 recites the term "substantially simultaneously." The Examiner alleged that the term "substantially" is a relative term which renders the claim indefinite. Further, the Examiner stated that "[t]he term 'substantially' is not defined by the claim, the specification does not provide a standard for ascertaining what is meant by 'substantially simultaneously', and one of ordinary skill in the art would not be

reasonably apprised of the scope of the claimed invention." Applicant respectfully disagrees.

The M.P.E.P. specifically provides that the term "substantially" is not indefinite, if its meaning can be determined from the specification and/or from what one of ordinary skill in the art would have understood the term to mean.

The term "substantially" is often used in conjunction with another term to describe a particular characteristic of the claimed invention. It is a broad term. *In re Nehrenberg*, 280 F.2d 161, 126 USPQ 383 (CCPA 1960). The court held that the limitation "to substantially increase the efficiency of the compound as a copper extractant" was definite in view of the general guidelines contained in the specification. *In re Mattison*, 509 F.2d 563, 184 USPQ 484 (CCPA 1975). The court held that the limitation "which produces substantially equal E and H plane illumination patterns" was definite because one of ordinary skill in the art would know what was meant by "substantially equal." *Andrew Corp. v. Gabriel Electronics*, 847 F.2d 819, 6 USPQ2d 2010 (Fed. Cir. 1988).

M.P.E.P. § 2173.05(b).

Thus, the M.P.E.P. provides that it is not necessary for a claim term to be defined by the claim. Here, the phrase "substantially simultaneously" is definite, because the present Specification clearly provides that "substantially simultaneously" means that "the sodium channel blockers, gabapentin and/or pregabalin are administered in sequence or at the same time so long as effective blood levels of the sodium channel blockers, gabapentin and pregabalin are achieved at the same time." Specification at page 23, lines 15-18.

Therefore, one of ordinary skill in the art would have understood the meaning of the term "substantially simultaneously." Applicant respectfully requests that this rejection be reconsidered and withdrawn.

***Rejection Under 35 U.S.C. § 103(a)***

The Examiner has rejected claims 10-21, 17-21, 34-45, and 50-52 under 35 U.S.C. § 103(a) as allegedly being obvious over Wang *et al.*, Published International Appl. No. WO 98/47869 ("Wang") in view of Rosenberg *et al.*, *The Clinical Journal of Pain* 13:251-255 (1997) ("Rosenberg"), and further in view of Bueno *et al.*, U.S. Patent No. 6,242,488 B1 ("Bueno") and Caruso *et al.*, U.S. Patent No. 6,187,338 ("Caruso"). Applicant respectfully traverses this rejection. A *prima facie* case of obviousness has not been established.

The Examiner stated:

The teaching of Wang differs from the claimed invention (i) mainly in the combination use of sodium channel blocker such as 4-(4'-fluorophenoxy) benzaldehyde semicarbazone and gabapentin in treating chronic pain, namely "trigeminal pain", "diabetic neuropathy" and "cancer pain"; (ii) the specific dosage amounts of each active ingredients, and (iii) the delivery of said combination in various dosage forms including oral, parenteral, intravenous, inmuscular [sic], intraperitoneal, transderal [sic] or bucal [sic] forms and the specific order of delivery of said combination.

With respect to the combination of sodium channel blocker [sic] such as 4-(4'fluorophenoxy) benzaldehyde semicarbazone and gabapentin for the treatment of chronic pain, [sic]

To incorporate such teaching into the teaching of Wang, would have been obvious in view of Rosenberg who teaches the use of gabapentin for treating chronic pain such as neuropathic pain (*e.g.*, neuralgia, diabetic neuropathy).

The references in combination make clear that the sodium channel blocker (*i.e.*, 4-(4'-fluorophenoxy) benzaldehyde semicarbazone) and gabapentin have been individually used for the treatment of chronic pain such as

neuropathic pain. It is obvious to combine two compositions each of which is taught by [sic] prior art to be useful for [sic] same purpose; idea [sic] of combining them flows logically from their having been individually taught in the prior art. The combination of active ingredient [sic] with the same character is merely the additive effect of each individual component. *See In re Kerkhoven, 205 USPQ 1069 (CCPA 1980).*

Office Action at pages 7-8.

As discussed above, Claims 10 and 52 have been amended to recite that the semicarbazone has the structure of Formula I. Claim 10 has also been amended to recite that "said first agent (a semicarbazone) and said second agent (gabapentin, pregabalin, salts thereof and combinations thereof) are present in synergistic amounts effective to treat or ameliorate neuropathic pain." Claim 52 has also been amended to recite "wherein said semicarbazone and at least one of gabapentin and pregabalin are administered in synergistic amounts effective to treat or ameliorate neuropathic pain."

To the extent Wang relates to carbocyclic and heterocyclic substituted semicarbazones and thiosemicarbazones, it is silent about a synergistic effect in treating or ameliorating neuropathic pain in combination with gabapentin, pregabalin, salts thereof and combinations thereof. Rosenberg, Bueno and Caruso fail to cure the deficiencies of Wang. Therefore, even in combination, Wang, Rosenberg, Bueno and Caruso would not have provided a reasonable expectation of success in providing a synergistic effect by combining a semicarbazone with gabapentin, pregabalin, salts thereof and combinations thereof.

A *prima facie* case of obviousness has not been established. Applicant respectfully requests that this rejection be reconsidered and withdrawn.


### *Conclusion*

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all of the presently outstanding objections and rejections.

Applicant believes that a full and complete reply has now been made to the outstanding Office Action and that, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided. Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



John M. Covert  
Attorney for Applicant  
Registration No. 38,759

Date: July 19, 2007

1100 New York Avenue, N.W.  
Washington, D.C. 20005-3934  
(202) 371-2600

698720\_1.DOC